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(51) International Patent Classification ⁷ : A61K 31/00		A2	(11) International Publication Number: WO 00/66103 (43) International Publication Date: 9 November 2000 (09.11.00)
<p>(21) International Application Number: PCT/US00/11449</p> <p>(22) International Filing Date: 1 May 2000 (01.05.00)</p> <p>(30) Priority Data: 60/198,238 4 May 1999 (04.05.99) US 09/552,037 19 April 2000 (19.04.00) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/552,037 (CON) Filed on 19 April 2000 (19.04.00)</p> <p>(71) Applicants (for all designated States except US): AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Girarda Farms, Madison, NJ 07840 (US). LIGAND PHARMACEUTICALS, INC. [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): GRUBB, Gary, S. [US/US]; 825 Briarwood Road, Newtown Square, PA 19073 (US). ZHI, Lin [CN/US]; 7794 Roan Road, San Diego, CA 92129 (US). JONES, Todd, K. [US/US]; 546 Marview Drive, Solana Beach, CA 92075 (US).</p>			
<p>TEGLEY, Christopher, M. [US/US]; 478 Thunderhead Street, Thousand Oaks, CA 91360 (US). PUWEN, Zhang [CN/US]; 7004 Oriole Court, Audubon, PA 19403 (US). FEN SOME, Andrew [GB/US]; 779 Trephanny Lane, Wayne, PA 19087 (US). VIET, Andrew, Q. [US/US]; Apt. L-200, 250 Beverly Boulevard, Upper Darby, PA 19082 (US). SANTILLI, Arthur, A. [US/US]; 1737 Sue Ellen Drive, Havertown, PA 19083 (US). TEREFENKO, Eugene, A. [US/US]; 266 Live Oak Drive, Quakertown, PA 18951 (US). WROBEL, Jay, E. [US/US]; 15 Rosetree Lane, Lawrenceville, NJ 08648 (US). EDWARDS, James, P. [US/US]; 8723 Hesby Court, San Diego, CA 92129 (US).</p> <p>(74) Agents: KODROFF, Cathy, A. et al.; Howson and Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).</p> <p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published Without international search report and to be republished upon receipt of that report.</p>			
(54) Title: CYCLIC REGIMENS USING CYCLIC UREA AND CYCLIC AMIDE DERIVATIVES			
<p style="text-align: center;">(I)</p>			
<p>(57) Abstract</p> <p>This invention concerns cyclic combination therapies using indoline derivatives which are progesterone receptor antagonists of general structure (I) wherein: A, B and D are N or CH, though not all can be CH; R¹ and R² are H, COR^A, NR^BCOR^A, or optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, or aryl groups; or R¹ and R² form a spirocyclic ring; R^A is H or optionally substituted alkyl, aryl, alkoxy, or aminoalkyl; R^B is H, alkyl alkyl; R³ is H, OH, NH₂, alkyl, alkenyl, or COR^C; R^C is H, alkyl, aryl, alkoxy, or aminoalkyl; R⁴ is benzene or a 5 or 6 membered heteroaromatic ring; R^E is H, alkyl, aryl, alkoxy, or aminoalkyl; R^G is H or alkyl; R^S is H or alkyl; W is O or a chemical bond; or a pharmaceutically acceptable salt thereof. These methods may be used for contraception or treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, or minimization of side effects or cyclic menstrual bleeding. Additional uses of the invention include stimulation of food intake.</p>			

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CYCLIC REGIMENS USING CYCLIC UREA
AND CYCLIC AMIDE DERIVATIVES

Field of the Invention

5 This invention relates to regimens of administering compounds which are antagonists of the progesterone receptor in combination with a progestin, an estrogen, or both.

Background of the Invention

10 Intracellular receptors (IR) form a class of structurally related gene regulators known as "ligand dependent transcription factors" (R. M. Evans, *Science*, 240, 889, 1988). The steroid receptor family is a subset of the IR family, including progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR).

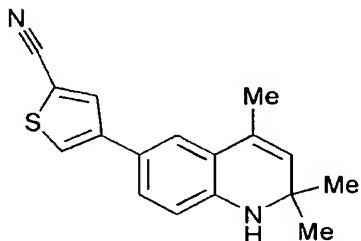
15 The natural hormone, or ligand, for the PR is the steroid progesterone, but synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, have been made which also serve as ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex binds to specific gene 20 promoters present in the cell's DNA. Once bound to the DNA the complex modulates the production of mRNA and protein encoded by that gene.

25 A compound that binds to an IR and mimics the action of the natural hormone is termed an agonist, whilst a compound which inhibits the effect of the hormone is an antagonist. PR agonists (natural and synthetic) are known to play an important role in the health of women. PR agonists are used in birth control formulations, typically in the presence of an ER agonist. ER agonists are used to treat the symptoms of menopause, but have been associated with a proliferative effect on the uterus which can lead to an increased risk of uterine cancers. Co-administration of a PR agonist reduces/ablates that risk.

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PR antagonists may also be used in contraception. In this context they may be administered alone (Ulmann, et al, *Ann. N.Y. Acad. Sci.*, **261**, 248, 1995), in combination with a PR agonist (Kekkonen, et al, *Fertility and Sterility*, **60**, 610, 1993) or in combination with a partial ER antagonist such as tamoxifen (WO 96/19997 A1, 5 July 4, 1996). PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz, et al, *Horm. Cancer*, 283, pub: Birkhaeuser, Boston, Mass., ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions such as fibroids (Murphy, et al, *J. Clin. Endo. Metab.*, **76**, 513, 1993) and endometriosis 10 (Kettel, et al, *Fertility and Sterility*, **56**, 402, 1991). PR antagonists may also be useful in hormone replacement therapy for post menopausal patients in combination with a partial ER antagonist such as tamoxifen (US 5719136). PR antagonists, such as mifepristone and onapristone, have been shown to be effective in a model of hormone dependent prostate cancer, which may indicate their utility in the treatment of this 15 condition in men (Michna, et al, *Ann. N.Y. Acad. Sci.*, **761**, 224, 1995).

Jones, et al, (U.S. Patent No. 5,688,810) describe the PR antagonist dihydroquinoline 1.

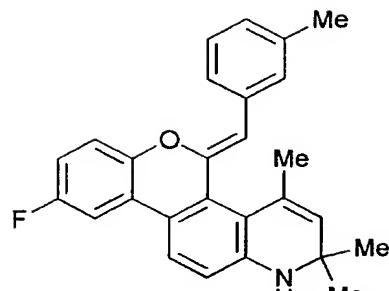


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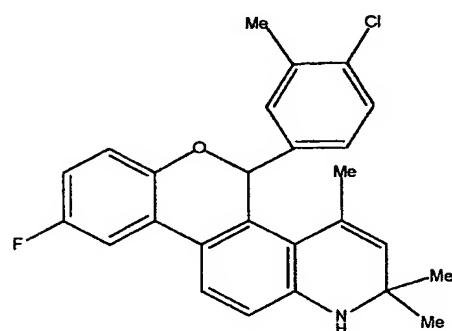
Jones, et al, described the enol ether 2 (U.S. Patent No. 5,693,646) as a PR ligand.

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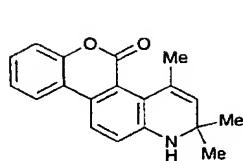
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Jones, *et al*, described compound 3 (U.S. Patent No. 5,696,127) as a PR
5 ligand.

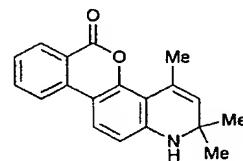


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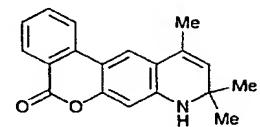
Zhi, *et al*, described lactones 4, 5 and 6 as PR antagonists (J. Med. Chem., 41,
10 291, 1998).



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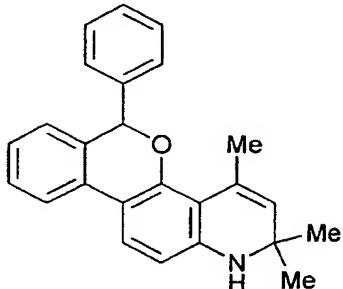
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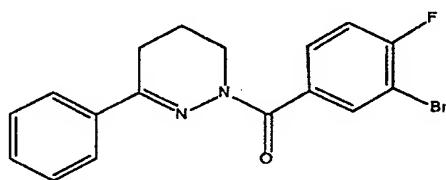
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Zhi, *et al.*, described the ether **7** as a PR antagonist (*J. Med. Chem.*, **41**, 291, 1998).



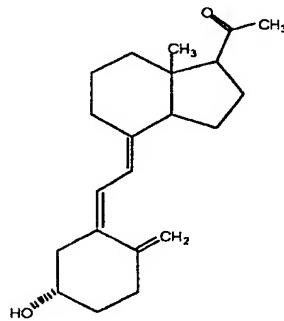
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5 Combs, *et al.*, disclosed the amide **8** as a ligand for the PR (*J. Med. Chem.*, **38**, 4880, 1995).



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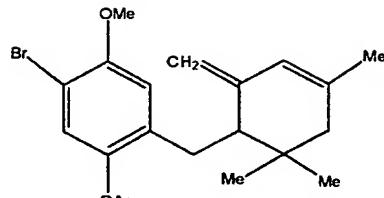
10 Perlman, *et. al.*, described the vitamin D analog **9** as a PR ligand (*Tet. Letters*, **35**, 2295, 1994).



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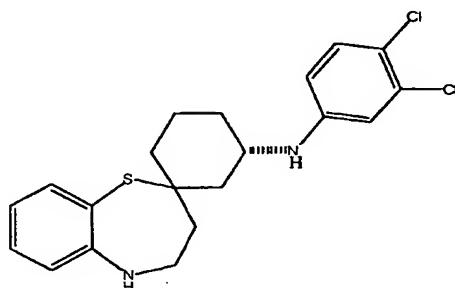
Hamann, *et al*, described the PR antagonist **10** (*Ann. N.Y. Acad. Sci.*, **761**, 383, 1995).



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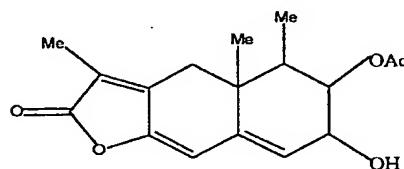
Chen, *et al*, described the PR antagonist **11** (Chen, *et al*, POI-37, 16th Int. Cong. Het. Chem., Montana, 1997).



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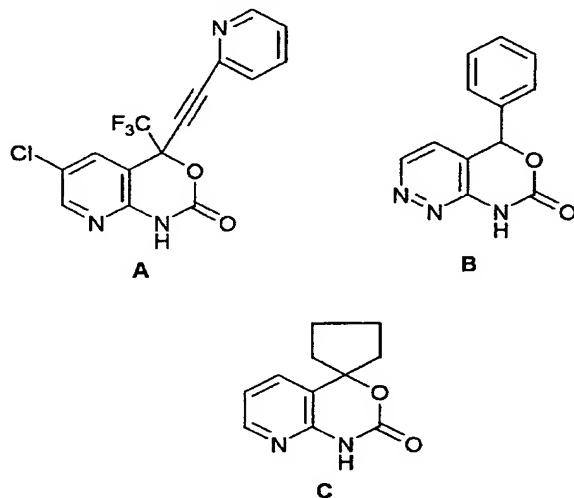
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Kurihara, *et. al.*, described the PR ligand **12** (*J. Antibiotics*, **50**, 360, 1997).

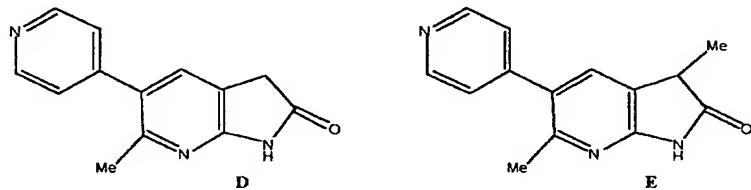


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The patent by Christ et al. (WO 9814436) claims cyclo amide such as compound **A** as inhibitors of HIV reverse transcriptase. Other prior art includes pyridazine cyclo amide such as compound **B** by Turck et al. (*Tetrahedron*, **49**(3), 599-606 (1993).) and compound such as **C** by Canonne et al. (*J. heterocyclic Chem.* **26**, 5 113(1989).). No activity data were reported in Turck's and Canonne' publications.



Regarding cyclic amides, Singh et al. and Kumar et al. (Singh et al. *J. Med. Chem.* **37**(2), 248-254(1994); Kumar et al. *J. Org. Chem.* **57**(25), 6995-6998(1992).) 10 disclose compounds such as **D** and **E** claimed as cAMP PDE III inhibitors.



U.S Patent No. 5,521,166 (Grubb) teaches cyclophasic hormonal regimens comprising an antiprogestin and a progestin wherein the progestin is administered in the alternating presence and absence of an antiprogestin. The disclosed regimens also provide for use of an estrogen for a period of from 2-4 days to prevent breakthrough bleeding.

Description of the Invention

This invention provides combination therapies and dosing regimens utilizing antiprogestational agents in combination with one or more progestational agents. This invention further provides methods of treatment and dosing regimens further utilizing in combination with these antiprogestins and progestins, an estrogen, such as ethinyl estradiol.

These regimens and combinations may be administered to a mammal to induce contraception or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. Additional uses of the invention include stimulation of food intake. The uses herein for the treatment and/or prevention of the conditions or diseases described above includes the continuous administration or periodic discontinuation of administration of the invention to allow for minimization of effect dose or minimization of side effects or cyclic menstrual bleeding.

The use of this invention for contraception includes administration, preferably orally, to a female of child bearing age an antiprogestin in combination with an estrogen or progestin or both. These administration regimens are preferably carried out over 28 consecutive days, with a terminal portion of the cycle containing administration of no progestins, estrogens or anti-progestins.

The progestins of these combinations may be administered alone or in combination with an estrogen for the first 14-24 days of the cycle, the progestins being administered at a dosage range equal in progestational activity to about 35 µg to about

150 µg levonorgestrel per day, preferably equal in activity to from about 35 µg to about 100 µg levonorgestrel per day. An antiprogestin may then be administered alone or in combination with an estrogen for a period of 1 to 11 days to begin on any cycle day between day 14 and 24. The anti-progestin in these combinations may be

5 administered at a dose of from about 2µg to about 50 µg per day and the estrogen may be administered at a dose of from about 10 µg to about 35 µg per day. In an oral administration, a package or kit containing 28 tablets will include a placebo tablet on those days when the antiprogestin or progestin or estrogen is not administered.

In a preferred embodiment of this invention, the progestins of this invention
10 may be administered alone or in combination with estrogen for the initial 18 to 21 days of a 28-day cycle, followed by administration of an antiprogestin, alone or in combination with an estrogen, for from 1 to 7 days.

The estrogen to be used in the combinations and formulations of this invention is preferably ethinyl estradiol.

15 Progestational agents useful with this invention include, but are not limited to, levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate. Among the preferred progestins for use in the combinations of this invention are levonorgestrel,
20 gestodene and trimegestone.

Examples of orally administered regimens of this invention over a 28 day cycle include administration of a progestational agent solely for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 100 µg of levonorgestrel. An antiprogestin compound of this invention may then be administered
25 at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28. It is most preferred that the daily dosages of each relevant active ingredient be incorporated into a combined, single daily dosage unit, totaling 28 daily units per 28-day cycle.

In another regimen, a progestational agent may be coadministered for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 150 µg levonorgestrel, preferably equal in activity to from about 35 to about 100 µg levonorgestrel, with an estrogen, such as ethinyl estradiol, at a daily dose range of 5 from about 10 to about 35 µg. This may be followed as described above with an antiprogestin administered at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28.

Still another regimen within the scope of this invention will include coadministration from days 1 to 21 of a progestational agent, the progestational agent, 10 preferably levonorgestrel, being administered at a daily dose equal in progestational activity to from about 35 to about 100 µg levonorgestrel, and an estrogen, such as ethinyl estradiol, at a daily dose range of from about 10 to about 35 µg. This will be followed on days 22 to 24 by coadministration of an antiprogestin (2 to 50 mg/day) 15 and an estrogen, such as ethinyl estradiol, at a daily dose of from about 10 to about 35 µg. From day 25 to day 28, this regimen may be followed by no administration or administration of a placebo.

This invention also kits or packages of pharmaceutical formulations designed for use in the regimens described herein. These kits are preferably designed for daily oral administration over a 28-day cycle, preferably for one oral administration per day, 20 and organized so as to indicate a single oral formulation or combination of oral formulations to be taken on each day of the 28-day cycle. Preferably each kit will include oral tablets to be taken on each the days specified, preferably one oral tablet will contain each of the combined daily dosages indicated.

According to the regimens described above, one 28-day kit may comprise:

25 a) an initial phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in progestational activity to about 35 to about 100 µg levonorgestrel;

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b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of this invention, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

5 c) optionally, a third phase of an orally and pharmaceutically acceptable placebo for the remaining days of the cycle in which no antiprogestin, progestin or estrogen is administered.

A preferred embodiment of this kit may comprise:

a) an initial phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably 10 equal in progestational activity to about 35 to about 100 µg levonorgestrel;

b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin compound of this invention, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

15 c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

Another 28-day cycle packaging regimen or kit of this invention comprises:

a) a first phase of from 18 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in activity to from about 35 to about 100 µg levonorgestrel, and, as an 20 estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and

b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of this invention at a daily dose of from about 2 to 50 mg; and

25 c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0-9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the kit described above may comprise:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal

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in activity to from about 35 to about 100 µg levonorgestrel, and, as an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and

b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin administered at a daily dose of from about 2 to 50 mg; and

5 c) optionally, a third phase of 4 daily dose units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

A further 28-day packaged regimen or kit of this invention comprises:

a) a first phase of from 18 to 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in activity to from about 35 to about 100 µg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg;

10 b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

15 c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0-9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the package or kit just described comprises:

20 a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably from about 35 to about 100 µg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg;

25 b) a second phase of 3 daily dose units for days 22 to 24, each dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

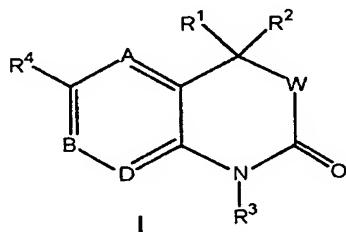
c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

In each of the regimens and kits just described, it is preferred that the daily dosage of each pharmaceutically active component of the regimen remain fixed in each particular phase in which it is administered. It is also understood that the daily dose units described are to be administered in the order described, with the first phase followed in order by the second and third phases. To help facilitate compliance with each regimen, it is also preferred that the kits contain the placebo described for the final days of the cycle. It is further preferred that each package or kit comprise a pharmaceutically acceptable package having indicators for each day of the 28-day cycle, such as a labeled blister package or dial dispenser packages known in the art.

10 In this disclosure, the terms anti-progestational agents, anti-progestins and progesterone receptor antagonists are understood to be synonymous. Similarly, progestins, progestational agents and progesterone receptor agonists are understood to refer to compounds of the same activity.

These dosage regimens may be adjusted to provide the optimal therapeutic response. For example, several divided doses of each component may be administered daily or the dose may be proportionally increased or reduced as indicated by the exigencies of the therapeutic situation. In the descriptions herein, reference to a daily dosage unit may also include divided units which are administered over the course of each day of the cycle contemplated.

20 Compounds of this invention which may be used as the anti-progestational agents in the kits, methods and regimens herein are those of the Formula I:



wherein:

A, B and D are N or CH, with the proviso that A, B and D can not all be CH;
R¹ and R² are independent substituents selected from H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, NR^BCOR^A;

5 or R¹ and R² are fused to form a spirocyclic ring selected from a), b) or c), each spirocyclic ring optionally substituted by from 1 to 3 C₁-C₃ alkyl groups:

10 a) a 3 to 8 membered spirocyclic alkyl ring;

b) a 3 to 8 membered spirocyclic alkenyl ring; or

c) an optionally substituted 3 to 8 membered heterocyclic ring containing one to three heteroatoms from the group including O, S and N; the spirocyclic rings of a), b) and c) being optionally substituted by from 1 to 4 groups selected from fluorine, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, C₁ to C₆ thioalkyl, -CF₃, -OH, -15 CN, NH₂, -NH(C₁ to C₆ alkyl), or -N(C₁ to C₆ alkyl)₂;

R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

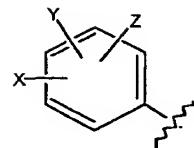
20 R^B is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, or COR^C;

25 R^C is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R⁴ is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:

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X is taken from the group including halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, OCOR^D, or NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy; or

R⁴ is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR^S and containing one or two independent substituents from the group including H, halogen, CN, NO₂ and C₁ to C₃ alkyl, C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, COR^F, or NR^GCOR^F;

R^F is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^G is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

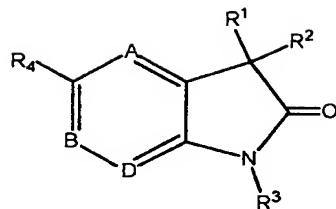
R^S is H or C₁ to C₃ alkyl;

W is O or a chemical bond;

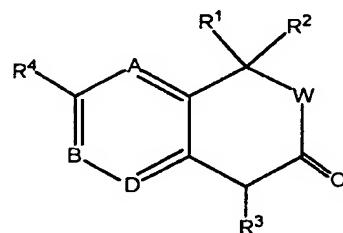
or a pharmaceutically acceptable salt thereof.

When W is a chemical bond, it is understood that Formula I exists as:

- 15 -



Preferred antiprogestin compounds are those of the formula:



5

wherein:

A, B and D are N or CH, with the proviso that A, B and D can not all be CH;

10 R¹ is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

R² is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or

15 R¹ and R² are fused to form the optionally substituted 3 to 8 membered spirocyclic alkyl, alkenyl or heterocyclic rings described above;

R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

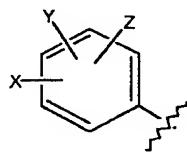
20 R^B is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

- 16 -

R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, or COR^C;

R^C is H, C₁ to C₄ alkyl, substituted C₁ to C₄ alkyl, aryl, substituted aryl, C₁ to C₄ alkoxy, substituted C₁ to C₄ alkoxy, C₁ to C₄ aminoalkyl, or substituted C₁ to C₄ aminoalkyl;

R⁴ is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



X is selected from halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, a 5 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, OCOR^D, or NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

Y and Z are independent substituents selected from H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy;

or

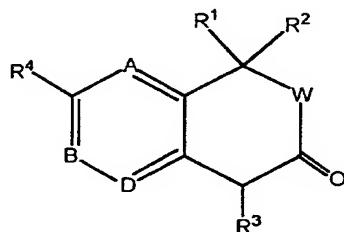
R⁴ is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR^S and containing one or two independent substituents from the group including H, halogen, CN, NO₂ and C₁ to C₃ alkyl, or C₁ to C₃ alkoxy;

R^S is H or C₁ to C₃ alkyl;

W is O or a chemical bond;

or a pharmaceutically acceptable salt thereof.

Still, more preferred antiprogestin compounds are those of the formula:



5 wherein:

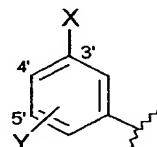
A, B and D are N or CH, with the proviso that A, B and D cannot all be CH;

R¹ = R² and are selected from the group of C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, or spirocyclic alkyl constructed by fusing R¹ and R² to form a 3 to 6 membered spirocyclic ring;

10 R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, or COR^C;

R^C is H, C₁ to C₄ alkyl, or C₁ to C₄ alkoxy;

R⁴ is a disubstituted benzene ring containing the substituents X, and Y as shown below:



15

X is selected from the group of halogen, CN, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, or C₁ to C₃ thioalkoxy;

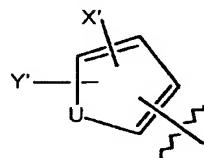
Y is a substituent on the 4' or 5' position from the group including H, halogen,

20 CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, or C₁ to C₃ thioalkoxy;

or

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R^4 is a five membered ring with the structure:



U is O , S , or NR^5 ;

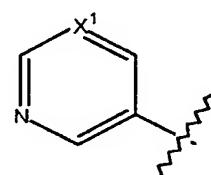
R^5 is H , or C_1 to C_3 alkyl, or C_1 to C_4 CO_2 alkyl;

5 X' is selected from halogen, CN , NO_2 , C_1 to C_3 alkyl, or C_1 to C_3 alkoxy;

Y' is selected from H and C_1 to C_4 alkyl;

or

R^4 is a six membered ring with the structure:



10

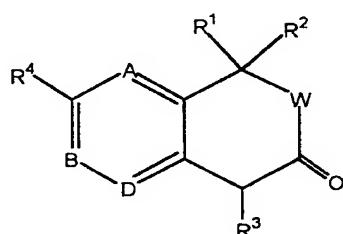
X^1 is N or CX^2 ;

X^2 is halogen, CN or NO_2 ;

or a pharmaceutically acceptable salt thereof.

15

Further preferred antiprogestational compounds include those of the formula:



- 19 -

wherein:

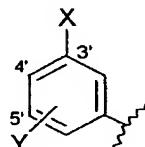
A, B and D are N or CH, with the proviso that A, B and D can not all be CH;

10 $R^1 = R^2$ and are selected from CH_3 and spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 6 membered spirocyclic ring;

R^3 is H, OH, NH_2 , CH_3 , substituted methyl, or COR^C ;

R^C is H, C_1 to C_3 alkyl, or C_1 to C_4 alkoxy;

15 R^4 is a disubstituted benzene ring containing the substituents X and Y as shown below:



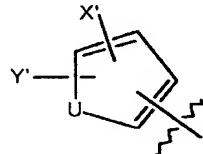
10

X is halogen, CN , methoxy, NO_2 , or 2-thiazole;

Y is a substituent on the 4' or 5' position selected from H and F;

or

15 R^4 is a five membered ring of the structure:



U is O, S, or NH;

X' is halogen, CN , or NO_2 ;

Y' is H or C_1 to C_4 alkyl;

20 W is O or a chemical bond;

or a pharmaceutically acceptable salt thereof.

The antiprogestin compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more

asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry in Formula I, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having one to eight carbon atoms, preferably one to six carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group with at least one carbon-carbon double bond and two to eight carbon atoms, preferably two to six carbon atoms; "alkynyl" group is intended to cover both straight- and branched-chain alkyl group with at least one carbon-carbon triple bond and two to eight carbon atoms, preferably two to six carbon atoms..

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as just described having one or more substituents from the group including halogen, CN, OH, NO₂, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon of alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

The term "aryl" is used herein to refer to an aromatic system which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include but not limited to phenyl, naphthyl, biphenyl, anthryl, tetrohydronaphthyl, phenanthryl.

The term "substituted aryl" refers to aryl as just defined having one to four substituents from the group including halogen, CN, OH, NO₂, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

The term "heterocyclic" is used herein to describe a stable 4- to 7-membered monocyclic or a stable multicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. The N and S atoms 5 may be oxidized. The heterocyclic ring also includes any multicyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. The heterocyclic ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, for example, tetrahydrofuran, 10 piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and isoquinoliny.

The term "substituted heterocyclic" is used herein to describe the heterocyclic just defined having one to four substituents selected from the group which includes 15 halogen, CN, OH, NO₂, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio. The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl. The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl. The term "alkylcarbonyl" is used herein 20 to refer to the RCO group, where R is alkyl or substituted alkyl. The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl. The term "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or substituted alkyl groups containing one to eight carbon atoms, which may be either same or different and the point of attachment is on the nitrogen 25 atom. "Halogen" refers to Cl, Br, F, or I.

The antiprogestin compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include, but are not limited to, the following salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and, as the case may be,

such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium in the form of esters, carbamates and other conventional "pro-drug" forms, which, when administered in such form, convert to the 5 active moiety *in vivo*.

These methods may be used for contraception or treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis, 10 polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, or minimization of side effects or cyclic menstrual bleeding. Additional uses of the invention include stimulation of food intake.

When the compounds are employed for the above utilities, they may be combined with one or more pharmaceutically acceptable carriers or excipients, for example, solvents, diluents and the like, and may be administered orally in such forms 15 as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic 20 medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

These active agents of the methods and regimens herein may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers 25 include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvents customarily employed in the preparation of pharmaceutical compositions

may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

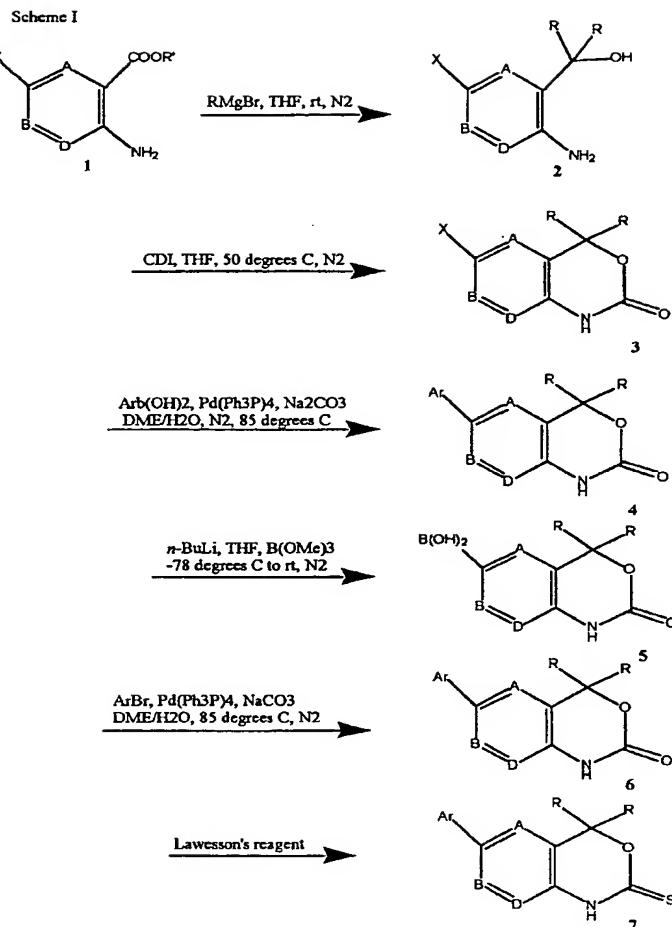
The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringe ability exists. It must be stable under conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The antiprogestin compounds of this invention can be prepared following the Schemes illustrated below:

As demonstrated in Scheme I, the antiprogestin compounds of this invention are generally prepared by employing the suitable coupling reaction as a final step. An appropriately substituted ortho-amino acid or its derivatives such as ethyl ester (X = Br, I, Cl, or a latent coupling precursor such as alkoxy group which can be converted into OTf group suitable in the coupling reaction) is treated with a suitable organo metallic reagent, e.g. Grignard reagent, in appropriate nonprotic solvents which

include but not limited to THF or ether to give ortho-amino carbinol **2** under an inert atmosphere such as argon or nitrogen at -78 °C to room temperature. Ring closure of carbinol **2** to yield oxazin-2-ones **3** is commonly effected by a condensing agent such as carbonyldiimidazole, phosgene, dimethylcarbonate, or diethylcarbonate in a suitable 5 nonprotic solvent such as THF at temperatures ranging from room temperature to 65 °C. The arylation of oxazin-2-ones **3** to yield **4** can be effected by various coupling reactions including Suzuki, Stille reactions etc.. These reactions are commonly performed in the presence of transition metallic catalyst, e.g., palladium or nickel complex often with phosphino ligands, e.g., Ph₃P, 1,1'-10 bis(diphenylphosphino)ferrocene, 1,2-bis(diphenylphosphino)ethane or palladium salt such as palladium acetate. Under this catalytic condition, an appropriately substituted nucleophilic reagent, e.g., aryl boronic acid, arylstannane, or aryl zinc compound, is coupled with oxazinones **3** to give compounds **4**. If a base is needed in the reaction, the commonly used bases include but not limited to sodium bicarbonate, sodium 15 carbonate, potassium phosphate, barium carbonate, potassium acetate, or cesium fluoride. The most commonly used solvents in these reactions include benzene, DMF, isopropanol, ethanol, DME, ether, acetone or a mixture of any one of these solvent and water. The coupling reaction is generally executed under an inert atmosphere such as nitrogen or argon at temperatures ranging from room temperature to 95 °C. 20 Oxazinones **3** can be converted into a nucleophile such as boronic acid which can be coupled with an appropriate electrophile, e.g., aryl bromide or aryl iodide, to yield **6** employing the coupling reaction condition as described above.

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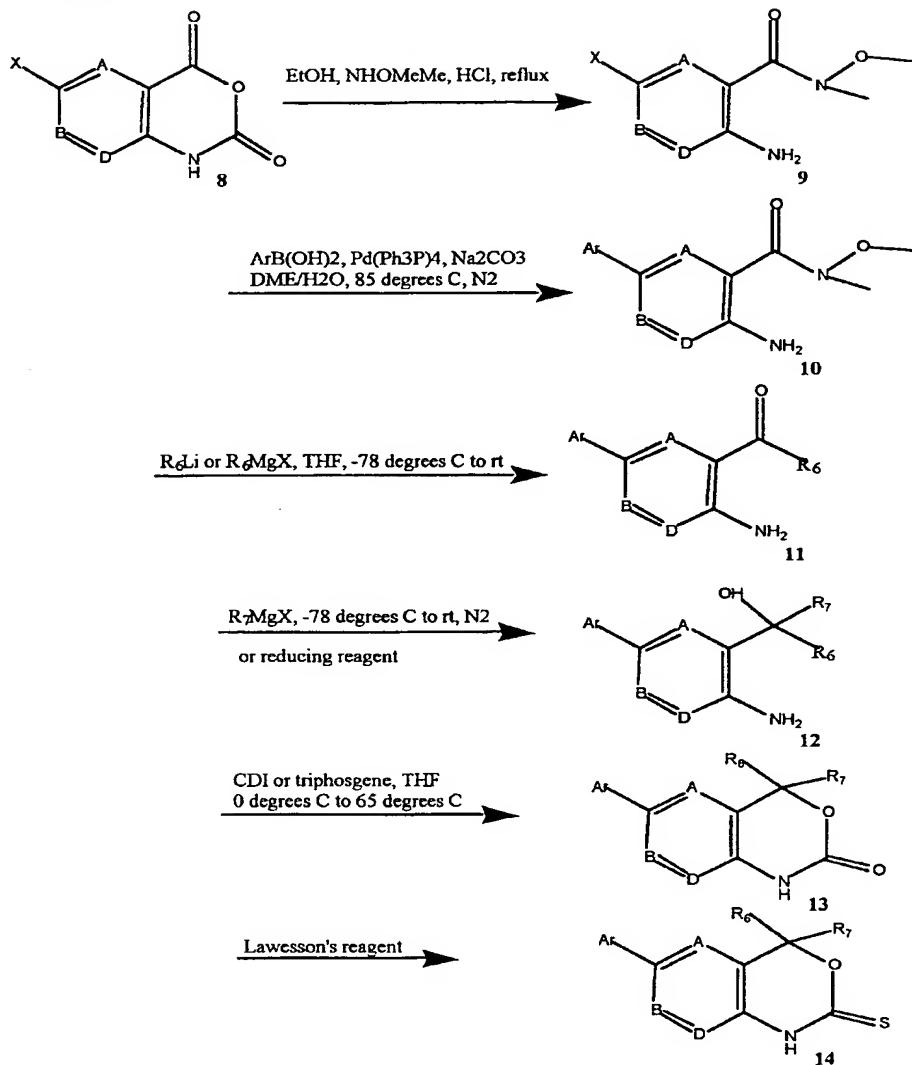
The transformation of 3 into 5 can be effected by treating 3 with an organo metallic reagent, e.g., *n*-BuLi, in a nonprotic solvent such as THF or ether followed by quenching the reaction solution with a suitable electrophile such as trimethyl borate, triisopropyl borate, bishexalkyl tin reagent, or zinc chloride at temperatures ranging from -78 °C to room temperature under an inert atmosphere such as argon or nitrogen. Conversion of carbamate 6 to thiocarbamate 7 can be readily effected by treatment of 6 with a suitable sulfur reagent such as P₂S₅ or Lawesson's reagent in a suitable non-

protic solvent such as toluene, chlorobenzene, benzene, or xylene under an inert atmosphere such as argon or nitrogen at the temperature of boiling solvent.

Scheme II describes the procedures to prepare oxazinones bearing two different substituents at position-4. The Weinreb amide **9** can be prepared from an 5 appropriately substituted isatoic anhydride when treated with *N*-, *O*-dimethylhydroxyl-amine hydrochloride salt in a protic solvent such as ethanol or isopropanol at reflux under an inert atmosphere such as argon or nitrogen. Coupling of amide **9** with an aryl electrophile such as aryl boronic acid or arylstannane to give **10** can be effected by employing a typical coupling reaction such as Suzuki, Stille coupling procedure in a 10 similar fashion as described for the preparation of oxazinones **4**. Treatment of Weinreb amide **10** with organo metallic compounds, e.g., alkylolithium, alkynyllithium, aryllithium, or their Grignard counterpart in a nonprotic solvent such as THF or ether under an inert atmosphere such as argon or nitrogen at -78°C to room temperature affords amino ketone **11**. Conversion of ketone **11** to carbinol **12** can be effected by 15 treatment of **10** with an organo metallic reagent such as alkyl, alkynyl, or aryl Grignard compound in a nonprotic solvent such as THF or ether under an inert atmosphere such as argon or nitrogen at -78°C to room temperature. Conversion of ketone **11** to carbinol **12** can also be effected by reduction of ketone group of **11** to the carbinol moiety of **12** using an appropriate reducing reagent such as lithium aluminum hydride, 20 sodium borohydride in a suitable solvent such as THF, ether, or anhydrous alcohol under an inert atmosphere in the temperature ranging from 0°C to the boiling point of the solvent. Ring closure of carbinol **12** to produce the compounds of this invention, 25 **13**, can be accomplished with condensing agents such as carbonyldiimidazole, phosgene, dimethylcarbonate, or diethylcarbonate in a suitable nonprotic solvent such as THF at temperatures ranging from room temperature to 65 °C. Conversion of carbamate **13** to thiocarbamate **14** can be readily effected by treatment of **13** with a suitable sulfur reagent such as P₂S₅ or Lawesson's reagent in a suitable nonprotic solvent such as toluene, chlorobenzene, benzene, or xylene under an inert atmosphere such as argon or nitrogen at the temperature of boiling solvent.

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Scheme II

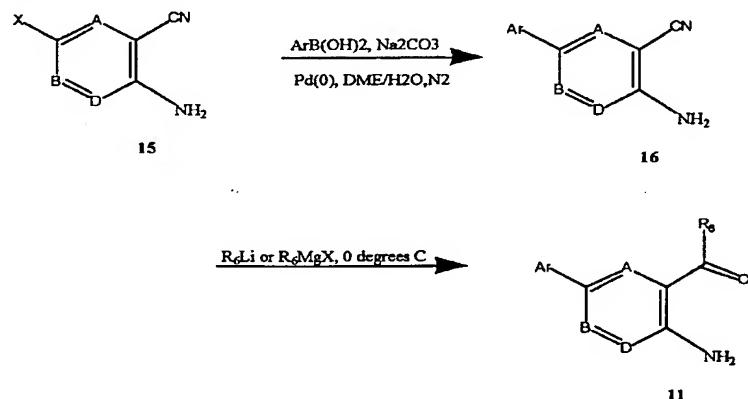


Alternatively, ortho-amino ketone 11 can be prepared by treatment of ortho-amino nitrile 16 with an organo metallic compound such as organo lithium reagent or Gringard reagent in a suitable solvent such as THF or ether under an inert atmosphere

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such as argon or nitrogen at temperatures ranging from -78 °C to room temperature as illustrated in Scheme III. Nitrile **16** can be readily prepared from an appropriately substituted nitrile such as bromobenzonitrile **15** using a suitable coupling reaction such as Stille or Suzuki protocol carried out in a similar fashion as described for the preparation of the Weinreb amide **10**.

Scheme III



The following non-limiting examples illustrate the compounds useful in the invention.

EXAMPLE 1

2-Amino-5-bromo-3-pyridine carboxylic acid

To a solution of 2-amino-nicotinic acid (10 g, 72.5 mmol) in acetic acid (70 mL) was dropwise added bromine (9.8 mL, 79.8 mmol) at room temperature under nitrogen. Upon completion of the reaction, the solvent was removed *in vacuo*, the residue triturated with ether and collected on a filter to give 2-amino-5-bromo-3-pyridine carboxylic acid as a yellow solid (15.7 g, 99%): mp 272 °C, (decomposed);

- 29 -

¹H-NMR (DMSO-d₆) δ 8.8-7.8 (bs, 2H), 8.44 (d, 1H, *J* = 2.48 Hz), 8.34 (d, 1H, *J* = 2.48 Hz); MS (EI) m/z 216/218 ([M +]⁺, 100%)

EXAMPLE 2

5

2-(2-Amino-5-bromo-pyridin-3-yl)-propan-2-ol

To a solution of 2-amino-5-bromo-3-pyridine carboxylic acid (5 g, 23 mmol) in THF (70 mL) at 0 °C was added methyl magnesium bromide (13.7 g, 115 mmol) under nitrogen. After addition, the reaction mixture was heated at 65 °C for 12 hours, cooled to room temperature and quenched with saturated aqueous ammonium chloride. The ethyl acetate was added and organic layer was separated, dried over sodium sulfate and concentrated. The residue was purified *via* flash chromatography to give 2-(2-amino-5-bromo-pyridin-3-yl)-propan-2-ol as a yellow solid (1.2 g, 23%): mp 107-108 °C; ¹H-NMR (DMSO-d₆) δ 7.89 (d, 1H, *J* = 2.3 Hz), 7.40 (d, 1H, *J* = 2.3 Hz), 6.28 (bs, 2H), 5.51 (s, 1H), 1.4 (s, 6H); MS (APCI) m/z 231 ([M + H]⁺, 100%).

10
15

EXAMPLE 3

6-Bromo-4,4'-dimethyl-1,4-dihydro-3-oxa-1,8-diaza-naphthalen-2-one

A mixture of 2-(2-amino-5-bromo-pyridin-3-yl)-propan-2-ol (0.86 g, 3.7 mmol) and 1,1'-carbonyldiimidazole (excess) in THF (10 mL) was heated at 35 °C 20 overnight. The reaction solution was cooled to room temperature, poured into ethyl acetate (200 mL), washed with 1 N HCl (2x50 mL), dried over sodium sulfate, and concentrated. The residue was purified by a flash chromatography (silica gel, 25% ethyl acetate/hexane) to afford 6-bromo-4,4'-dimethyl-1,4-dihydro-3-oxa-1,8-diaza-naphthalen-2-one (0.9 g, 94%) as a white solid: mp 251-252 °C; ¹H-NMR (DMSO-d₆) δ 10.9 (s, 1H), 8.32 (d, 1H, *J* = 2.19 Hz), 8.0 (d, 1H, *J* = 2.22 Hz), 1.6 (s, 6H); MS (EI) m/z 256 ([M]⁺, 80%); Anal. Calc. For C₉H₉BrN₂O₂: C, 42.05, H, 3.53, N, 10.90. Found: C, 42.15, H, 3.65, N, 10.80.

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EXAMPLE 4

6-(3-Chloro-phenyl)-4,4-dimethyl-1,4-dihydro-3-oxa-1,8-diaza-naphthalene-2-one

A mixture of 6-bromo-4,4'-dimethyl-1,4-dihydro-3-oxa-1,8-diaza-naphthalen-5 2-one (0.1 g, 0.39 mmol), 3-chlorophenyl boronic acid (0.075 g, 0.47 mmol), tetrakis(triphenylphosphine)-palladium (0) (0.023 g, 0.02 mmol), and sodium carbonate (0.1 g, 0.94 mmol) in DME (8 mL) and water (5 mL) was subject to a blanket of nitrogen for 15 minutes at 50 °C and then was heated at 85 °C for 30 minutes. The reaction was cooled to room temperature and ethyl acetate (100 mL) 10 was added. The organic layer washed with aqueous ammonium chloride (2x50 mL) and with brine (50 mL), dried over magnesium sulfate and concentrated. The product was dissolved in dichloromethane and passed through a plug of magnesol. The solvent was removed and the clear oil obtained triturated with ether (25 mL) to give 6-(3-chloro-phenyl)-4,4-dimethyl-1,4-dihydro-3-oxa-1,8-diaza-naphthalene-2-one as a 15 white solid (0.087 g, 80%): mp 214-215 °C; ¹H-NMR (DMSO-d₆) δ 10.9 (s, 1H), 8.56 (d, 1H, J = 2.35 Hz), 8.06 (d, 1H, J = 2.35 Hz), 7.86 (t, 1H, J = 2.35 Hz), 7.72 (td, 1H, J = 9.4, 2.35 Hz), 7.54-7.44 (m, 2H), 1.69 (s, 6H); MS (ESI) m/z 289 ([M+H]⁺, 100%); Anal. Calc. For C₁₇H₁₇NO₃: C, 62.40, H, 4.54, N, 9.70. Found: C, 60.53, H, 4.40, N, 9.21.

20

EXAMPLE 5

6-Chloro-3-nitro-pyridine-2-carbonitrile

A mixture of 2, 6-dichloro-3-nitropyridine and cuprous cyanide in 1-methyl-2-pyrrolidinone was quickly heated to 180 °C and maintained at that temperature for 15 25 minutes with vigorous stirring. The mixture was cooled to -10 °C and the deep brown solution was poured into ice water (3.5 L) and stirred for 30 min. The flocculent brown precipitate was collected and washed with H₂O. After drying for about 1.5 h, the moist solid was extracted with boiling toluene (3x300 mL). The combined toluene extracts were washed with H₂O, brine, and dried (MgSO₄), concentrated. The crude

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product was crystallized from EtOAc/hexane to afford the title compound: mp 115-117 °C; ¹H NMR (DMSO-d₆) δ 8.16 (dd, 1H, J = 8.7, 3.0 Hz), 8.82 (d, 1H, J = 9.0 Hz); MS (EI) *m/z* 183/185 (M+H)⁺; Anal. Calc. For C₆H₂ClN₃O₂: C, 39.26, H, 1.10, N, 22.89. Found: C, 39.47, H, 1.38, N, 22.77.

5

EXAMPLE 6

3-Amino-6-chloro-pyridine-2-carbonitrile

To a solution of 2,6-dichloro-3-nitropyridine(4.8 g, 26.15 mmol) in MeOH (60 mL) and concentrated HCl (25 mL) was slowly added iron powder(5.12g, 91.53 mmol). After the completion of addition, the mixture was refluxed for 45 minutes and poured into a 700 mL of H₂O. Filtration of the resulting slurry gave a dull yellow solid. The filtrate was made basic with concentrated NH₄OH, the resulting slurry was filtered and both the solid and the filtrates were extracted with ether. The combined extracts were dried (MgSO₄) and evaporated to give the title compound as a creamy solid (2.8g, 58%): mp 162-165 °C which was used in next step without further purification.

EXAMPLE 7

1-(3-Amino-6-chloro-pyridin-2-yl)-ethanone

To a solution of 3-amino- 6-chloro-pyridine-2-carbonitrile (0.75g, 4.88 mmol) in anhydrous THF (25 mL) under nitrogen was added a solution of methylmagnesium bromide (3M in ether, 8.1 mL, 24.3 mmol). The reaction mixture was stirred for 30 minutes and then slowly quenched with H₂O, treated with 5N HCl solution. The mixture was extracted with ethyl acetate (3x100 mL) and organic extracts were washed with brine, and dried (MgSO₄). After removal of solvent, the residue was purified by chromatography using EtOAc/hexane mixture (1:3) as eluent to afford the title compound as a greenish crystalline solid: (0.71g, 85%): mp: 108-110 °C. ¹H NMR (DMSO-d₆) δ 2.51 (s, 3H), 7.28-7.39 (m, 4H); MS(ESI) *m/z* 171/173 (M+H)⁺;

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Anal. Calc. For C₇H₇ClN₂O: C, 49.28, H, 4.14, N, 16.14. Found: C, 49.70, H, 4.03, N, 16.41.

EXAMPLE 8

5

1-(3-Amino-6-chloro-pyridin-2-yl)-propan-2-ol

To a solution of 1-(3-amino-6-chloro-pyridin-2-yl)-ethanone in anhydrous THF under N₂ was added a solution of methylmagnesium bromide (3N in ether,). The resulting reaction mixture was stirred at room temperature for 4 h, then slowly quenched with H₂O, treated with 0.5 N HCl and stirred for 30 minutes, diluted with 10 ethyl acetate, washed with brine, dried (MgSO₄), concentrated, and chromatographed using a mixture of EtOAc/Hexane (3.5: 6.5) to afford the title compound as a white crystals (0.45g, 82%): mp: 118-121 °C. ¹H NMR(DMSO-d₆) δ 1.45(s, 6H), 3.35(s, 1H), 5.51(s, 1H), 5.68(s, 1H), 7.02(s, 1H); MS((+)APCI) m/z 187/189 (M+H)⁺; Anal. Calc. For C₈H₁₁ClN₂O: C, 51.48, H, 5.94, N, 15.01. Found: C, 51.22, H, 5.99, N, 14.47.

15

EXAMPLE 9

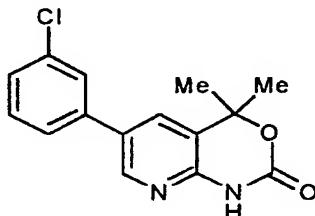
6-Chloro-4,4-dimethyl-1,4-dihydro-3-oxa-1,5-diaza-naphthalen-2-one

20

To a solution of 1-(3-amino-6-chloro-3-nitro-pyridin-2-yl)-propan-2-ol (0.3g, 1.67 mmol) in anhydrous THF (20 mL) was added a solution of 1,1'-carbonyldiimidazole (0.68g, 4.12 mmol) in anhydrous THF (10 mL). The reaction mixture was heated under reflux for 3 h. The reaction mixture was treated with 0.5N HCl, washed with brine, H₂O, dried (MgSO₄), concentrated and crystallized from EtOAc/hexane to obtain the title compound as a white crystalline solid (0.2g, 56%): 25 mp 175-178 °C. ¹H NMR(DMSO-d₆) δ 1.60 (s, 6H), 7.30 (d, 1H, J= 8.41 Hz), 7.41 (d, 1H, J = 8.41 Hz), 10.47 (s, 1H); MS((+)APCI) m/z 213 (M+H)⁺; Anal. Calc. For C₉H₉ClN₂O₂: C, 50.84, H, 4.27, N, 13.17. Found: C, 50.99, H, 4.28, N, 12.98.

EXAMPLE 10

The compounds of this invention were tested in the relevant assay as described below and their potency are in the range of 0.01 nM to 5 μ M in the *in vitro* assays and 0.001 to 300 mg/kg in the *in vivo* assays. The selected example is example 4.



5

Example 4, hPR CV-1, IC₅₀ = 0.8 μ M

A. In-vitro biology

The in-vitro biology is determined by (1) competitive

10 Radioligand Binding: using the A-form of the human progesterone receptor with progesterone as the radioligand; (2) co-transfection assay, which provides functional activity expressed as agonist EC₅₀ and Antagonist IC₅₀ values; (3) a T47D cell proliferation, which is a further functional assay which also provides agonist and antagonist data; and (4) T47D cell alkaline phosphatase assay, which is a further functional assay which also provides agonist and antagonist data.

15

1. hPR Binding assay - This assay is carried out in accordance with: Pathirana, C.; Stein, R.B.; Berger, T.S.; Fenical, W.; Ianiro, T.; Mais, D.E.; Torres, A.; Glodman, M.E., *Nonsteroidal human progesterone receptor modulators from the marine alga cymoplia barbata*, J. Steroid Biochem. Mol. Biol.,

20 1992, **41**, 733-738.

2. PRE-luciferase assay in CV-1 cells

The object of this assay is to determine a compound's progestational or antiprogestational potency based on its effect on PRE-luciferase

reporter activity in CV-1 cells co-transfected with human PR and PRE-luciferase plasmids. The materials methods used in the assay are as follows.

a. Medium: The growth medium was as follows:

DMEM (BioWhittaker) containing 10% (v/v) fetal bovine serum (heat inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL). The experimental medium was as follows: DMEM (BioWhittaker), phenol red-free, containing 10% (v/v) charcoal-stripped fetal bovine serum (heat-inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

10 b. Cell culture, transfection, treatment, and luciferase assay

Stock CV-1 cells are maintained in growth medium. Co-transfection is done using 1.2×10^7 cells, 5 mg pLEM plasmid with hPR-B inserted at Sph1 and BamH1 sites, 10 mg pGL3 plasmid with two PREs upstream of the

15 luciferase sequence, and 50 mg sonicated calf thymus DNA as carrier DNA in 250 ml. Electroporation is carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II. After electroporation, cells are resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 μ l. Following overnight incubation, the medium is changed to experimental medium. Cells are then treated with reference or test

20 compounds in experimental medium. Compounds are tested for antiprogestational activity in the presence of 3 nM progesterone. Twenty-four hr. after treatment, the medium is discarded, cells are washed three times with D-PBS (GIBCO, BRL). Fifty μ l of cell lysis buffer (Promega, Madison, WI) is added to each well and the plates are shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase

25 activity is measured using luciferase reagents from Promega.

c. Analysis of Results:

Each treatment consists of at least 4 replicates. Log transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight

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the effects of outliers. EC_{50} or IC_{50} values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear response analyses.

d. Reference Compounds:

5 Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC_{50} or IC_{50} values are calculated.

10 **Table 1. Estimated EC_{50} , standard error (SE), and 95% confidence intervals (CI) for reference progestins from three individual studies**

Compound	Exp.	<u>EC_{50}</u>		<u>95% CI</u>	
		(nM)	SE	lower	upper
Progesterone	1	0.616	0.026	0.509	0.746
	2	0.402	0.019	0.323	0.501
	3	0.486	0.028	0.371	0.637
Trimegestone	1	0.0075	0.0002	0.0066	0.0085
	2	0.0081	0.0003	0.0070	0.0094
	3	0.0067	0.0003	0.0055	0.0082

25 **Table 2. Estimated IC_{50} , standard error (SE), and 95% confident interval (CI) for the antiprogestin, RU486 from three individual studies**

Compound	Exp.	<u>IC_{50}</u>		<u>95% CI</u>	
		(nM)	SE	lower	upper
RU486	1	0.028	0.002	0.019	0.042
	2	0.037	0.002	0.029	0.048
	3	0.019	0.001	0.013	0.027

Progestational activity: Compounds that increase PRE-luciferase activity significantly ($p<0.05$) compared to vehicle control are considered active.

Antiprogestational activity: Compounds that decrease 3 nM progesterone induced PRE-luciferase activity significantly ($p<0.05$)

5 EC₅₀: Concentration of a compound that gives half-maximal increase PRE-luciferase activity (default-nM) with SE.

IC₅₀: Concentration of a compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity (default-nM) with SE.

3. T47D cell proliferation assay

10 The objective of this assay is the determination of progestational and antiprogestational potency by using a cell proliferation assay in T47D cells. A compound's effect on DNA synthesis in T47D cells is measured. The materials and methods used in this assay are as follows.

a. Growth medium: DMEM:F12 (1:1)

15 (GIBCO, BRL) supplemented with 10% (v/v) fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Treatment medium: Minimum Essential

20 Medium (MEM) (#51200-038GIBCO, BRL) phenol red-free supplemented with 0.5% charcoal stripped fetal bovine serum, 100U/ml penicillin, 200 mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

c. Cell culture

25 Stock T47 D cells are maintained in growth medium. For BrdU incorporation assay, cells are plated in 96-well plates (Falcon, Becton Dickinson Labware) at 10,000 cells/well in growth medium. After overnight incubation, the medium is changed to treatment medium and cells are cultured for an additional 24 hr before treatment.

Stock compounds are dissolved in appropriate vehicle (100% ethanol or 50% ethanol/50% DMSO), subsequently diluted in treatment medium and added to the cells. Progestin and antiprogestin reference compounds are run in full dose-response

curves. The final concentration of vehicle is 0.1%. In control wells, cells receive vehicle only. Antiprogestins are tested in the presence of 0.03 nM trimegestone, the reference progestin agonist. Twenty-four hours after treatment, the medium is discarded and cells are labeled with 10 mM BrdU (Amersham Life Science, Arlington Heights, IL) in treatment medium for 4 hr.

5 d. Cell Proliferation Assay

At the end of BrdU labeling, the medium is removed and BrdU incorporation is measured using a cell proliferation ELISA kit (#RPN 250, Amersham Life Science) according to manufacturer's instructions. Briefly, cells are fixed in an 10 ethanol containing fixative for 30 min, followed by incubation in a blocking buffer for 30 min to reduce background. Peroxidase-labeled anti-BrdU antibody is added to the wells and incubated for 60 min. The cells are rinsed three times with PBS and incubated with 3,3'5,5'-tetramethylbenzidine (TMB) substrate for 10-20 min depending upon the potency of tested compounds. Then 25 μ l of 1 M sulfuric acid is 15 added to each well to stop color reaction and optical density is read in a plate reader at 450 nm within 5 min.

6 e. Analysis of Results:

Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is 20 used to downweight the effects of outliers. EC₅₀ or IC₅₀ values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

7 f. Reference Compounds:

25 Trimegestone and medroxyprogesterone acetate (MPA) are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC₅₀ or IC₅₀ values are calculated.

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Table 3. Estimated EC₅₀, standard error (SE), and 95% confidence intervals (CI) for individual studies

5	Compound	Exp	EC ₅₀	<u>95% CI</u>		
			(nM)	SE	lower	upper
10	Trimegestone	1	0.017	0.003	0.007	0.040
		2	0.014	0.001	0.011	0.017
		3	0.019	0.001	0.016	0.024
15	MPA	1	0.019	0.001	0.013	0.027
		2	0.017	0.001	0.011	0.024

Table 4. Estimated IC₅₀, standard error, and 95% confident interval for the antiprogestin, RU486

15	Compound	Exp	IC ₅₀	<u>95% CI</u>		
			(nM)	SE	lower	upper
20	RU486	1	0.011	0.001	0.008	0.014
		2	0.016	0.001	0.014	0.020
		3	0.018	0.001	0.014	0.022

EC₅₀: Concentration of a compound that gives half-maximal increase in BrdU incorporation with SE; IC₅₀: Concentration of a compound that gives half-maximal decrease in 0.1 trimegestone induced BrdU incorporation with SE

25 4. T47D cell alkaline phosphatase assay

The purpose of this assay is to identify progestins or antiprogestins by determining a compound's effect on alkaline phosphatase activity in T47D cells. The materials and methods used in this assay are as follows.

a. Culture medium: DMEM:F12 (1:1) (GIBCO, BRL)

30 supplemented with 5% (v/v) charcoal stripped fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100 µg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

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b. Alkaline phosphatase assay buffer:

- I. 0.1 M Tris-HCl, pH 9.8, containing 0.2% Triton X-100
- II. 0.1 M Tris-HCl, pH 9.8 containing 4 mM p-nitrophenyl phosphate (Sigma).

5

c. Cell Culture and Treatment:

Frozen T47D cells were thawed in a 37°C water bath and diluted to 280,000 cells/ml in culture medium. To each well in a 96-well plate (Falcon, Becton Dickinson Labware), 180 µl of diluted cell suspension was added. Twenty µl of reference or test compounds diluted in the culture medium was then added 10 to each well. When testing for progestin antagonist activity, reference antiprogestins or test compounds were added in the presence of 1 nM progesterone. The cells were incubated at 37°C in a 5% CO₂/humidified atmosphere for 24 hr.

d. Alkaline Phosphatase Enzyme Assay:

At the end of treatment, the medium was removed 15 from the plate and fifty µl of assay buffer I was added to each well. The plates were shaken in a titer plate shaker for 15 min. Then 150 µl of assay buffer II was added to each well. Optical density measurements were taken at 5 min intervals for 30 min at a test wavelength of 405 nM.

e. Analysis of Results: Analysis of dose-response data

20 For reference and test compounds, a dose response curve is generated for dose (X-axis) vs. the rate of enzyme reaction (slope) (Y-axis). Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC₅₀ or IC₅₀ values are calculated from the 25 retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

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f. Reference Compounds:

Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose response curves and the EC₅₀ or IC₅₀ values are calculated.

5

Table 5. Estimated EC₅₀, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three independent experiments

10	Compound	Exp.	EC50	95% CI		
			(nM)	SE	lower	upper
15	Progesterone	1	0.839	0.030	0.706	0.996
		2	0.639	0.006	0.611	0.669
		3	1.286	0.029	1.158	1.429
20	Trimegestone	1	0.084	0.002	0.076	0.091
		2	0.076	0.001	0.072	0.080
		3	0.160	0.004	0.141	0.181

25 Table 6. Estimated IC₅₀, standard error, and 95% confident interval for the reference antiprogestin RU486 from three independent experiments

25	Compound	Exp	IC 50	95% CI		
			(nM)	SE	lower	upper
30	RU486	1	0.103	0.002	0.092	0.115
		2	0.120	0.001	0.115	0.126
		3	0.094	0.007	0.066	0.134

B. In-vivo Biology

The primary in-vivo assay is the rat decidualization model, which may be used to determine progestational effects of both agonists and antagonists. The secondary in-

vivo assay is the rat ovulation inhibition model, which is under development, and hence the protocol is un-available.

1. Rat decidualization assay The objective of this procedure is used to evaluate the effect of progestins and antiprogestins on rat uterine decidualization and 5 compare the relative potencies of various test compounds. The materials and methods used in this assay are as follows.

a. Methods: Test compounds are dissolved in 100% ethanol and mixed with corn oil (vehicle). Stock solutions of the test compounds in oil (MazolaTM) are then prepared by heating (~80 °C) the mixture to evaporate ethanol.

10 Test compounds are subsequently diluted with 100% corn oil or 10% ethanol in corn oil prior to the treatment of animals. No difference in decidual response was found when these two vehicles were compared.

b. Animals (RACUC protocol #5002)

Ovariectomized mature female Sprague-Dawley rats (~60-day old and 230g) 15 are obtained from Taconic (Taconic Farms, NY) following surgery. Ovariectomy is performed at least 10 days prior to treatment to reduce circulating sex steroids. Animals are housed under 12 hr light/dark cycle and given standard rat chow and water ad libitum.

c. Treatment

20 Rats are weighed and randomly assigned to groups of 4 or 5 before treatment. Test compounds in 0.2 ml vehicle are administered by subcutaneous injection in the nape of the neck or by gavage using 0.5 ml. The animals are treated once daily for seven days. For testing antiprogestins, animals are given the test compounds and a EC₅₀ dose of progesterone (5.6 mg/kg) during the first three days 25 of treatment. Following decidual stimulation, animals continue to receive progesterone until necropsy four days later.

d. Dosing

Doses are prepared based upon mg/kg mean group body weight. In all studies, a control group receiving vehicle is included. Determination of

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dose-response curves is carried out using doses with half log increases (e.g. 0.1, 0.3, 1.0, 3.0 mg/kg...).

e. Decidual induction

Approximately 24 hr after the third injection, decidualization 5 is induced in one of the uterine horns by scratching the antimesometrial luminal epithelium with a blunt 21 G needle. The contralateral horn is not scratched and serves as an unstimulated control. Approximately 24 hr following the final treatment, rats are sacrificed by CO₂ asphyxiation and body weight measured. Uteri are removed and 10 trimmed of fat. Decidualized (D-horn) and control (C-horn) uterine horns are weighed separately.

f. Analysis of Results:

The increase in weight of the decidualized uterine horn is calculated by D-horn/C-horn and logarithmic transformation is used to maximize 15 normality and homogeneity of variance. The Huber M-estimator is used to down weight the outlying transformed observations for both dose-response curve fitting and one-way analysis of variance. JMP software (SAS Institute, Inc.) is used for both one-way ANOVA and non-linear dose-response analyses.

g. Reference Compounds:

All progestin reference compounds were run in full dose- 20 response curves and the EC₅₀ for uterine wet weight were calculated.

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Table 7. Estimated EC₅₀, standard error (SE), and 95% confidence intervals for individual studies

5	Compound	Exp	EC ₅₀		95% CI	
			(mg/kg, s.c.)	SE	lower	upper
10	Progesterone	1	5.50	0.77	4.21	7.20
		2	6.21	1.12	4.41	8.76
15	3-Ketodesogestrel	1	0.11	0.02	0.07	0.16
		2	0.10	0.05	0.11	0.25
		3	0.06	0.03	0.03	0.14
20	Levonorgestrel	1	0.08	0.03	0.04	0.16
		2	0.12	0.02	0.09	0.17
	MPA	3	0.09	0.02	0.06	0.13
		4	0.09	0.02	0.06	0.14
	MPA	1	0.42	0.03	0.29	0.60
		2	0.39	0.05	0.22	0.67
	3	0.39	0.04	0.25	0.61	

Table 8. Estimated average EC₅₀, standard error, and 95% confidence intervals for dose-response curves of 3 reference compounds

25	Compound	EC50		95% CI	
		(mg/kg, s.c.)	SE	lower	upper
	Progesterone	5.62	0.62	4.55	7.00
	3-Ketodesogestrel	0.10	0.02	0.07	0.14
30	Levonorgestrel	0.10	0.01	0.08	0.12

Table 9. Estimated IC₅₀, standard error, and 95% confident interval for the antiprogestin, RU 486

5	Compound	IC ₅₀		95% CI	
		Exp.	(mg/kg, p.o.)	SE	lower upper
	RU 486	1	0.21	0.07	0.05 0.96
		2	0.14	0.02	0.08 0.27

Concentration: Compound concentration in assay(default-mg/kg body weight)

10 Route of administration: Route the compound is administered to the animals

Body weight: Mean total animal body weight (default-kg)

D-horn: Wet weight of decidualized uterine horn (default-mg)

C-horn: Wet weight of control uterine horn (default-mg)

Decidual response: [(D-C)/C]x100%

15 Progestational activity: Compounds that induce decidualization significantly (p<0.05) compared to vehicle control are considered active

Antiprogestational activity: Compounds that decrease EC₅₀ progesterone induced decidualization significantly (p<0.05)

EC₅₀ for uterine weight: Concentration of compound that gives half-maximal increase in decidual response (default-mg/kg)

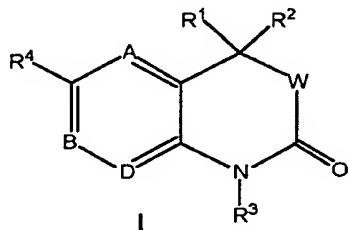
20 IC₅₀ for uterine weight: Concentration of compound that gives half-maximal decrease in EC₅₀ progesterone induced decidual response (default-mg/kg)

25 All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

What is Claimed:

1. A method of contraception which comprises administering to a female of child bearing age for 28 consecutive days:

- a first phase of from 14 to 24 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel;
- a second phase of from 1 to 11 daily dosage units, at a daily dosage of from about 2 to 50 mg, of an antiprogestin compound of Formula I:



wherein:

A, B and D are N or CH, with the proviso that A, B and D can not all be CH;

R¹ and R² are independent substituents selected from H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, NR^BCOR^A;

or R¹ and R² are fused to form a spirocyclic ring selected from a), b) or c), each spirocyclic ring optionally substituted by from 1 to 3 C₁-C₃ alkyl groups:

- a 3 to 8 membered spirocyclic alkyl ring;
- a 3 to 8 membered spirocyclic alkenyl ring; or
- an optionally substituted 3 to 8 membered heterocyclic ring containing one to three heteroatoms from the group including O, S and N; the spirocyclic rings of

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a), b) and c) being optionally substituted by from 1 to 4 groups selected from fluorine, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, C₁ to C₆ thioalkyl, -CF₃, -OH, -CN, NH₂, -NH(C₁ to C₆ alkyl), or -N(C₁ to C₆ alkyl)₂;

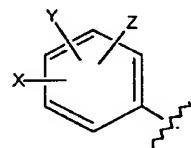
R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^B is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, or COR^C;

R^C is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R⁴ is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



X is taken from the group including halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, OCOR^D, or NR^ECOR^D;

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R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy;

or

R^4 is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR⁵ and containing one or two independent substituents from the group including H, halogen, CN, NO₂ and C₁ to C₃ alkyl, C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, COR^F, or NR^GCOR^F;

R^F is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^G is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R^5 is H or C₁ to C₃ alkyl;

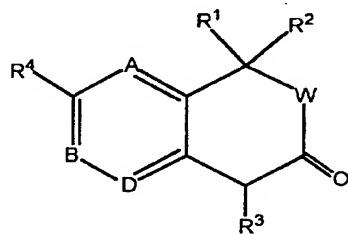
Q is O, S, NR⁶, or CR⁷R⁸;

W is O or a chemical bond; or a pharmaceutically acceptable salt thereof; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo for the remaining days of the 28 consecutive days

in which no antiprogestin, progestin or estrogen is administered; wherein the total daily dosage units of the first, second and third phases equals 28.

2. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:



wherein:

A, B and D are N or CH, with the proviso that A, B and D can not all be CH;

R¹ is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

R² is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or

R¹ and R² are fused to form the optionally substituted 3 to 8 membered spirocyclic alkyl, alkenyl or heterocyclic rings described above;

R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

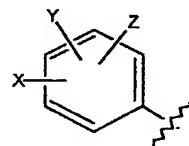
- 49 -

R^B is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R^3 is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, or COR^C;

R^C is H, C₁ to C₄ alkyl, substituted C₁ to C₄ alkyl, aryl, substituted aryl, C₁ to C₄ alkoxy, substituted C₁ to C₄ alkoxy, C₁ to C₄ aminoalkyl, or substituted C₁ to C₄ aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



X is selected from halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, a 5 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, OCOR^D, or NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

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Y and Z are independent substituents selected from H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy;
or

R⁴ is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR⁵ and containing one or two independent substituents from the group including H, halogen, CN, NO₂ and C₁ to C₃ alkyl, or C₁ to C₃ alkoxy;

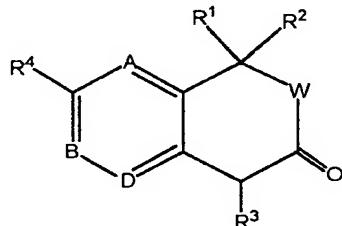
R⁵ is H or C₁ to C₃ alkyl;

Q is O, S, NR⁶, or CR⁷R⁸;

W is O or a chemical bond;

or a pharmaceutically acceptable salt thereof.

3. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:



wherein:

A, B and D are N or CH, with the proviso that A, B and D cannot all be CH;

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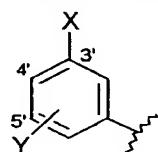
$R^1 = R^2$ and are selected from the group of C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 3 to 6 membered spirocyclic ring;

R^3 is H , OH , NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, or COR^C ;

R^C is H , C_1 to C_4 alkyl, or C_1 to C_4 alkoxy;

R^4 is selected from a), b) or c):

a) R^4 is a benzene ring of the formula:

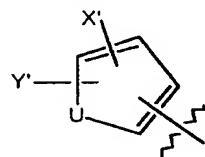


X is selected from the group of halogen, CN , C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, or C_1 to C_3 thioalkoxy;

Y is a substituent on the 4' or 5' position from the group including H , halogen, CN , NO_2 , C_1 to C_3 alkoxy, C_1 to C_4 alkyl, or C_1 to C_3 thioalkoxy;

or

b) R^4 is a five membered ring of the structure:



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U is O, S, or NR⁵;

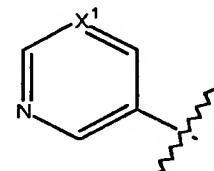
R⁵ is H, or C₁ to C₃ alkyl, or C₁ to C₄ CO₂alkyl;

X' is selected from halogen, CN, NO₂, C₁ to C₃ alkyl, or C₁ to C₃ alkoxy;

Y' is selected from H and C₁ to C₄ alkyl;

or

c) R⁴ is a six membered ring of the structure:

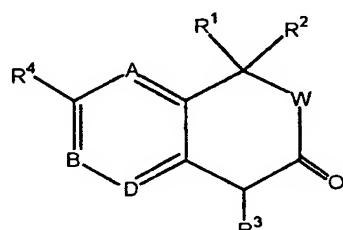


X¹ is N or CX²;

X² is halogen, CN or NO₂;

or a pharmaceutically acceptable salt thereof.

4. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:



wherein:

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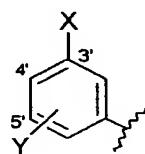
A, B and D are N or CH, with the proviso that A, B and D can not all be CH;

R¹ = R² and are selected from CH₃ and spirocyclic alkyl constructed by fusing R¹ and R² to form a 6 membered spirocyclic ring;

R³ is H, OH, NH₂, CH₃, substituted methyl, or COR^C;

R^C is H, C₁ to C₃ alkyl, or C₁ to C₄ alkoxy;

R⁴ is a disubstituted benzene ring containing the substituents X and Y as shown below:



X is halogen, CN, methoxy, NO₂, or 2-thiazole;

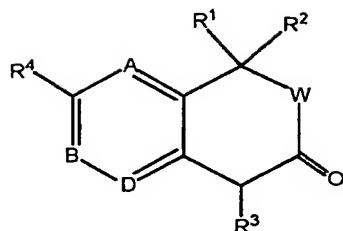
Y is a substituent on the 4' or 5' position selected from H or F;

W is O or a chemical bond;

or a pharmaceutically acceptable salt thereof.

5. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:

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wherein:

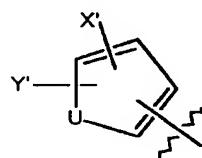
A, B and D are N or CH, with the proviso that A, B and D can not all be CH;

R¹ = R² and are selected from CH₃ and spirocyclic alkyl constructed by fusing R¹ and R² to form a 6 membered spirocyclic ring;

R³ is H, OH, NH₂, CH₃, substituted methyl, or COR^C;

R^C is H, C₁ to C₃ alkyl, or C₁ to C₄ alkoxy;

R⁴ is a five membered ring of the structure:



U is O, S, or NH;

X' is halogen, CN, or NO₂;

Y' is H or C₁ to C₄ alkyl;

W is O or a chemical bond;

or a pharmaceutically acceptable salt thereof.

6. A method of Claim 1 wherein the antiprogestin compound is 6-(3-Chloro-phenyl)-4,4-dimethyl-1,4-dihydro-3-oxa-1,8-diaza-naphthalene-2-one or a pharmaceutically acceptable salt thereof.

7. The method of Claim 1 wherein the progestational agent is selected from the group of levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate.

8. A method of Claim 1 which comprises administering to a female of child bearing age consecutively over a 28 day cycle:

- a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel;
- b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and
- c) optionally, 4 daily dosage units of an orally and pharmaceutically acceptable placebo to be administered on each day of the 28-day cycle following the first phase and second phase.

9. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

- a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and
- c) optionally, an orally and pharmaceutically acceptable placebo for each remaining day of the 28 consecutive days.

10. A method of contraception of Claim 15 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

- a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of 3 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and
- c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

11. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

- a) a first phase of from 18 to 21 daily dosage units containing a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg
- b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and
- c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo, the total of the daily dosage units being 28.

12. A method of contraception of Claim 11 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

- a) a first phase of 21 daily dosage units, each daily dosage unit containing a progestational agent at a daily dose equal in progestational activity to about 35 to about 100 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg
- b) a second phase of 3 daily dose, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

13. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

14. A pharmaceutically useful kit adapted for daily oral administration of Claim 13 which comprises:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel;

b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

15. A pharmaceutically useful kit adapted for daily oral administration which comprises:

- a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and
- c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

16. A pharmaceutically useful kit adapted for daily oral administration of Claim 15 which comprises:

- a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of three daily dosage units of an antiprogestin of Claim 1 administered at a daily dose of from about 2 to 50 mg; and
- c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

17. A pharmaceutically useful kit adapted for daily oral administration which comprises:

- a) a first phase of from 18 to 21 daily dosage units, each daily dosage unit comprising a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg
- b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

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c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;
wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

18. A pharmaceutically useful kit adapted for daily oral administration of Claim 17 which comprises:

- a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 μ g levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μ g
- b) a second phase of 3 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μ g; and
- c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 November 2000 (09.11.2000)

PCT

(10) International Publication Number
WO 00/66103 A3

(51) International Patent Classification⁷: A61K 45/06, 31/57, 31/565, A61P 15/18, A61K 31/495, 31/12 // (A61K 31/57, 31:495, 31:565) (A61K 31/57, 31:12, 31:565)

Wayne, PA 19087 (US). VIET, Andrew, Q. [US/US]; Apt. L-200, 250 Beverly Boulevard, Upper Darby, PA 19082 (US). SANTILLI, Arthur, A. [US/US]; 1737 Sue Ellen Drive, Havertown, PA 19083 (US). TERESENKO, Eugene, A. [US/US]; 266 Live Oak Drive, Quakertown, PA 18951 (US). WROBEL, Jay, E. [US/US]; 15 Rosetree Lane, Lawrenceville, NJ 08648 (US). EDWARDS, James, P. [US/US]; 8723 Hesby Court, San Diego, CA 92129 (US).

(21) International Application Number: PCT/US00/11449

(22) International Filing Date: 1 May 2000 (01.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/198,238 4 May 1999 (04.05.1999) US
09/552,037 19 April 2000 (19.04.2000) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/552,037 (CON)
Filed on 19 April 2000 (19.04.2000)

(71) Applicants (for all designated States except US): AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralta Farms, Madison, NJ 07840 (US). LIGAND PHARMACEUTICALS, INC. [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US).

(72) Inventors; and
(75) Inventors/Applicants (for US only): GRUBB, Gary, S. [US/US]; 825 Briarwood Road, Newtown Square, PA 19073 (US). ZHI, Lin [CN/US]; 7794 Roan Road, San Diego, CA 92129 (US). JONES, Todd, K. [US/US]; 546 Marview Drive, Solana Beach, CA 92075 (US). TEGLEY, Christopher, M. [US/US]; 478 Thunderhead Street, Thousand Oaks, CA 91360 (US). PUWEN, Zhang [CN/US]; 7004 Oriole Court, Audubon, PA 19403 (US). FENSOME, Andrew [GB/US]; 779 Trephanny Lane,

(74) Agents: KODROFF, Cathy, A. et al.; Howson and Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

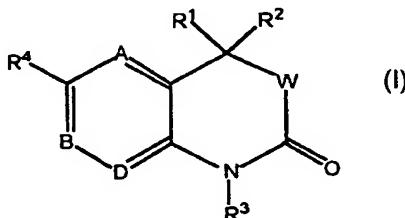
Published:

— With international search report.

(88) Date of publication of the international search report:
5 April 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CONTRACEPTIVE COMPOSITIONS CONTAINING CYCLIC UREA AND AMIDE DERIVATIVES



(57) Abstract: This invention concerns cyclic combination therapies using indoline derivatives which are progesterone receptor antagonists of general structure (I) wherein: A, B and D are N or CH, though not all can be CH; R¹ and R² are H, COR^A, NR^BCOR^A, or optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, or aryl groups; or R¹ and R² form a spirocyclic ring; R^A is H or optionally substituted alkyl, aryl, alkoxy, or aminoalkyl; R^B is H, alkyl alkyl; R³ is H, OH, NH₂, alkyl, alkenyl, or COR^C; R^C is H, alkyl, aryl, alkoxy, or aminoalkyl; R⁴ is benzene or a 5 or 6 membered heteroaromatic ring; R^E is H, alkyl, aryl, alkoxy, or aminoalkyl; R^G is H or alkyl; R^S is H or alkyl; W is O or a chemical bond; or a pharmaceutically acceptable salt thereof. These methods may be used for contraception or treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, or minimization of side effects or cyclic menstrual bleeding. Additional uses of the invention include stimulation of food intake.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 00/11449

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/57 A61K31/565 A61P15/18 A61K31/495
A61K31/12 // (A61K31/57, 31:495, 31:565), (A61K31/57, 31:12, 31:565)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, SCISEARCH, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 43 30 234 A (SCHERING AG) 9 March 1995 (1995-03-09) column 1, line 1 - line 30 claims 1-8	1-18
A	WO 96 15794 A (BALANCE PHARMACEUTICALS INC) 30 May 1996 (1996-05-30) page 6, line 15 -page 7, line 23	1-18
A	WO 97 49407 A (AKZO NOBEL NV ;COELINGH BENNINK HERMAN JAN TI (NL); VERBOST PIETER) 31 December 1997 (1997-12-31) page 2, line 29 -page 3, line 6	1-18
A	US 5 521 166 A (GRUBB GARY S) 28 May 1996 (1996-05-28) claim 1 column 2, line 41 - line 60	1-18
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

28 November 2000

Date of mailing of the international search report

05.01.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bonzano, C

INTERNATIONAL SEARCH REPORT

Inte
al Application No
PCT/US 00/11449

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 733 902 A (SCHNEIDER MARTIN) 31 March 1998 (1998-03-31) column 1, line 13 - line 19	1-18
A	DE 43 44 463 A (SCHERING AG) 29 June 1995 (1995-06-29) page 2, line 1 - line 16	1-18
A	US 5 696 133 A (HAMANN LAWRENCE G ET AL) 9 December 1997 (1997-12-09) claims 1,4,5	1,6-18
A	JHALANI, VINOD K. ET AL: "A convenient synthesis of 5-keto-6-methyl-5,6-dihydro-1,6-naphthyrid ine" INDIAN J. CHEM., SECT. B (1983), 22B(9), 916, XP000965424 the whole document	1-5

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US 00/11449**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 00/11449

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 7-18 (partially)

To provide a contraceptive composition, where a first phase is a progestational agent, and a second phase is an antiprogestinic compound, with a structure as defined in claim 1.

2. Claims: 2-6, 7-18 (partially)

To provide a contraceptive composition, where a first phase is a progestational agent, and a second phase is an antiprogestinic compound, with a structure as defined in claim 2.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 00 A1449

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5,7-18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Present claims 1,6,8-18 relate to a compound defined by reference to a desirable characteristic or property, namely the progestational activity. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the combinations of the compounds specifically mentioned in claim 7, with due regard to the general idea underlying the present invention.

Claims searched completely: none.

Claims searched incompletely: 1-18.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT
Information on patent family members

Inte
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